

REMARKS

The Official Action of November 6, 2008, and the references cited therein have been carefully considered. The Applicants respectfully request reconsideration of the application in view of the following remarks.

Status of the Application

This application was filed on October 14, 2004, as a U.S. National Phase application under 35 U.S.C. § 371 of PCT Application No. PCT/US03/11956, filed April 17, 2003, which claims priority under 35 U.S.C. § 119 from US Application No. 60/373,734, filed April 18, 2002. A Request for Continued Examination was submitted on September 5, 2008.

Claims Under Consideration

Claim 29 has been incorporated into Claim 28 and Claim 29 has been canceled. Claims 42 and 43 have been amended to correct typographical errors. Claims 28 and 30-46 are pending in the application.

Rejection of Claims 28-46 for Obviousness over Dorn et al. (U.S. Patent No. 5,719,147)

Claims 28-46 stand rejected under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147). The Applicants respectfully traverse this rejection and provide the following comments.

The Applicants respectfully assert that U.S. Patent No. 5,719,147 does not disclose or suggest the claimed invention. Nor would U.S. Patent No. 5,719,147 have motivated or enabled one skilled in the art to prepare the subject compounds in accordance with the claimed invention. The Examiner has failed to demonstrate the specific motivation in U.S. Patent No. 5,719,147 that would have motivated or directed one of ordinary skill in the art to prepare and utilize the subject compound in accordance with the claimed invention. Applicants respectfully submit that the Examiner has not made a prima facie case of obviousness, such that a showing of secondary indicia of non-obviousness such as unexpected results would be required. Even if the Examiner has established a prima facie case of obviousness, the present invention provides secondary indicia of non-obviousness such as unexpected results relative to the disclosure of U.S. Patent No. 5,719,147.

The Examiner stated:

The prior art [U.S. Patent No. 5,719,147] generically teaches alkylation of morpholinyl nitrogen (column 58) [generic scheme] with a specific embodiment to the preparation of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine (e.g. column 104, Example 75) with 79% yield, which requires cyclization of the product obtained from the generic scheme shown above to produce the triazole substituted final product.

Multiple embodiments disclose species for the generic reaction above: i.e. processes of alkylating the morpholinyl nitrogen (optionally followed by cyclization to form triazole) which use a variety of reagents, reaction conditions, etc. See representative embodiments noted below:

Example 17 - column 75 teaches use of DMF and anhydrous potassium carbonate

Example 45 - column 88 teaches drying and further heating at 140-150 by refluxing in xylenes.

... The instant reaction is a species encompassed by the generic teaching of the prior art.

... The generic teaching provided by the prior art disclosure, and the numerous embodiments, suggest to one of ordinary skill to practice the instantly claimed process with a reasonable expectation of success. The motivation would be to practice different processes of making the instantly claimed product of formula Ia which has utility.

It is noted that the specific limitations that are not expressly taught by the totality of the disclosed embodiments of US 5,719,147 do not add patentability to the claimed process.

Therefore, the instant claims are prima facie obvious over the disclosure of US 5,719,147. The rationale that supports the conclusion of obviousness is taken from MPEP 2141 and MPEP 2143, excerpts below:

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product was not of innovation but of ordinary skill and common sense.

No claims allowed.

Disclosure in U.S. Patent No. 5,719,147

U.S. Patent No. 5,719,147 discloses at Example 75, column 104, processes for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine ["aprepitant"] in 79% yield starting from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine, by using the procedure of Example 70, column 102, wherein:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine is reacted with:

N-methylcarboxy-2-chloro-acetamidrazone, and

N,N-diisopropylethylamine in acetonitrile at room temperature for 20 hours, to give:

2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine, which is:
heated in xylenes at reflux for 2 hours.

U.S. Patent No. 5,719,147 discloses at Example 17, column 75, a processes for obtaining the compound 4-(3-(1,2,4-triazolo)methyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine by:

reacting 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine with anhydrous potassium carbonate in DMF and N-formyl-2-chloroacetamidrazone.

U.S. Patent No. 5,719,147 discloses at Example 45, columns 88-89, a processes for obtaining the compound 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine by:

heating a solution of 4-(2-N-methylcarboxyacetamidrazono)-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine in xylenes at reflux.

Claimed Invention

The process disclosed in U.S. Patent No. 5,719,147 is very different from the presently claimed process.

As more fully recited in the claims, the claimed process for obtaining the compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3H-1,2,4-triazol-3-one [aka. "aprepitant"] comprises, e.g.:

reacting the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine with:

N-methylcarboxy-2-chloro-acetamidrazone, and

an inorganic base, in the presence of toluene and a polar aprotic solvent,

to give:

2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine, which is then:

cyclized by heating.

Differences Between U.S. Patent No. 5,719,147 and the Claimed Invention

U.S. Patent No. 5,719,14 does not teach any of the following reaction conditions in the context of preparing aprepitant:

- (1) the use of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;
- (2) the temperature of the cyclization process;
- (3) the use of toluene;
- (4) the use of an inorganic base (such as potassium carbonate); or
- (5) the use of a polar aprotic solvent (such as dimethylsulfoxide or dimethylformamide).

Applicants respectively submit that there would have been no motivation nor guidance in U.S. Patent No. 5,719,147 for one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention. The Examiner has not provided a sufficient factual basis to support the assertion that one of ordinary skill in the art would have been motivated by U.S. Patent No. 5,719,147 to have conducted the subject process in accordance with the claimed invention.

Consideration of the Claimed Invention as a Whole

Applicants respectfully request that the Examiner consider the claimed invention as a whole. Applicants respectfully request that the Examiner consider the claimed process in its entirety, including each and every element of the claimed process, as well as how each and every element relates to all of the other elements in the claimed process to prepare the compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3H-1,2,4-triazol-3-one ["aprepitant"].

Applicants respectfully submit that one of ordinary skill in the art would not have utilized such disclosure in U.S. Patent No. 5,719,147 that concerns different reaction processes and synthetic manipulations to provide the claimed invention.

There is no teaching whatsoever in U.S. Patent No. 5,719,147 that the conditions employed for such diverse chemical processes to prepare structurally different compounds should be employed in the context of each of the claimed reaction steps to prepare the subject compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3H-1,2,4-triazol-3-one in accordance with the claimed process. One of ordinary skill in the art would have been presented with a vast number of potential options because U.S. Patent No. 5,719,147 would have not given any indication regarding which parameters were critical, nor which direction among the many possible choices would have been successful.

(1) The Use of the Hydrochloride Salt of 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine:

There would have been no motivation in U.S. Patent No. 5,719,147 to have used the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine. In fact, Example 75 (with reference to Example 70) of U.S. Patent No. 5,719,147 teaches away from the present invention by indicating that the free base of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine should be employed.

There would have been no guidance in U.S. Patent No. 5,719,147 to have used the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine in accordance with the claimed process to prepare aprepitant with respect to any alkylation reaction, let alone the claimed process. None of the experimental procedures in U.S. Patent No. 5,719,147 employ the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine or the hydrochloride salt of any similar phenylethoxy-(3-phenyl)-morpholine compound as starting material in any comparable alkylation reaction.

Applicants respectfully request that the Examiner consider the disclosure in U.S. Patent No. 5,719,147 that teaches away from using the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine. In particular, Example 75 of U.S. Patent No. 5,719,147 teaches away from the present invention by indicating that the free base of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine should be employed for the alkylation reaction.

(2) The Temperature of the Cyclization Process:

There would have been no motivation in U.S. Patent No. 5,719,147 to have conducted the cyclization process at a temperature of about 140-150°C. Example 75 (by reference to Example 70) indicates that 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl)morpholine was prepared by heating 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-N-methylcarboxy-acetamidrazono)morpholine in 15 ml a mixture of xylenes at reflux for 2 hours. The CRC Handbook of Chemistry and Physics indicates that the boiling point of o-xylene is 144°C, the boiling point of m-xylene is 139°C, and the boiling point of p-xylene is 138°C. There is no indication that the process conditions in Example 75 of heating at reflux in a mixture of xylenes would have actually corresponded to a temperature of 140-150°C and, alternatively, there would have been no direction regarding how the temperature should have been changed.

The Examiner noted that U.S. Patent No. 5,719,147 discloses at Example 45, columns 88-89, a processes for obtaining the compound 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine by heating a solution of 4-(2-N-methylcarboxy-acetamidrazono)-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine in xylenes at reflux. These reaction conditions of heating in xylenes at reflux to cyclize the 2-N-methylcarboxy-acetamidrazono into an oxo-triazolo ring on the 2-(S)-(3,5-dichlorobenzyloxy)-3-

(S)-phenyl-morpholine compound are comparable to the conditions disclosed in Example 75. The reaction conditions in Example 45 are less relevant than the conditions disclosed in Example 75, however, because they are employed in the context of a different compound 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine, not a prepitane.

(3) The Use of Toluene

There would have been no motivation in U.S. Patent No. 5,719,147 to use toluene, rather than xylenes. U.S. Patent No. 5,719,147 does not disclose or suggest the use of toluene in any reactions comparable to the claimed process. In fact, Example 75 and similar disclosure in U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the xylenes should be employed as the reaction solvent for the alkylation reaction.

(4) The Use of An Inorganic Base

There would have been no motivation in U.S. Patent No. 5,719,147 to use an inorganic base, rather than the organic base such as N,N-diisopropylethylamine. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that an organic base such as N,N-diisopropylethylamine should have been employed.

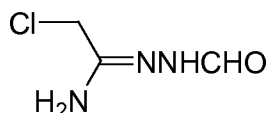
Example 75 (with reference to Example 70) discloses the use of N,N-diisopropylethylamine in acetonitrile to prepare 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine. Applicants respectfully submit that one of ordinary skill in the art would have considered N,N-diisopropylethylamine [i.e. $\text{NH}(\text{CH}(\text{CH}_3)_2)_2$] to be an organic base, and not an inorganic base.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 17, column 75, are not relevant to the process conditions of the present claims.

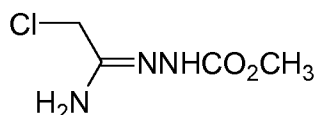
Example 17, column 75, discloses a process for obtaining the compound 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine by reacting 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine with anhydrous potassium carbonate in DMF and N-formyl-2-chloroacetamidrazone followed by heating at 120°C.

Applicants note that the present claims are directed to the preparation of a morpholine compound that bears a 5-oxo-1,2,4-triazolo ring, whereas the process of Example 17, column 75 describes the preparation of a 1,2,4-triazolo ring (i.e. oxo-substituted triazolo ring vs. triazolo ring).

Example 17 discloses the reaction of a morpholine starting material with N-formyl-2-chloroacetamidrazone:



In contrast, the present claims relate to reaction of the starting material with N-methylcarboxy-2-chloro-acetamidrazone:



Accordingly, the reaction conditions disclosed in Example 17, column 75, for alkylation with N-formyl-2-chloroacetamidrazone are not applicable to the present claims which involve alkylation with N-methylcarboxy-2-chloroacetamidrazone.

Applicants respectfully request that the Examiner consider the disclosure in U.S. Patent No. 5,719,147 that teaches away from using an inorganic base. In particular, Example 75 of U.S. Patent No. 5,719,147 teaches away from the present invention which uses an inorganic base by indicating that an organic base such as N,N-diisopropylethylamine should be employed for the alkylation reaction.

(5) The Use of Specific Solvents

There would have been no motivation in U.S. Patent No. 5,719,147 to use a specific solvent which is selected from dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, acetonitrile, N,N-dimethylacetamide and hexamethylphosphoramide, rather than acetonitrile. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the acetonitrile would have been required.

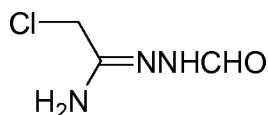
Example 75 (with reference to Example 70) discloses the use of N,N-diisopropylethylamine in acetonitrile to prepare 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 17, column 75, are not relevant to the process conditions of the present claims.

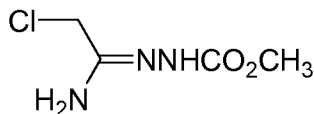
Example 17, column 75, discloses a processes for obtaining the compound 4-(3-(1,2,4-triazolo)methyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine by reacting 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine with anhydrous potassium carbonate in DMF and N-formyl-2-chloroacetamidrazone followed by heating at 120°C.

Applicants note that the present claims are directed to the preparation of a morpholine compound that bears a 5-oxo-1,2,4-triazolo ring, whereas the process of Example 17, column 75 describes the preparation of a 1,2,4-triazolo ring (i.e. oxo-substituted triazolo ring vs. triazolo ring).

Example 17 discloses the reaction of a morpholine starting material with N-formyl-2-chloroacetamidrazone:



In contrast, the present claims relate to reaction of the starting material with N-methylcarboxy-2-chloro-acetamidrazone:



Accordingly, the reaction conditions disclosed in Example 17, column 75, for alkylation with N-formyl-2-chloroacetamidrazone are not applicable to the present claims which involve alkylation with N-methylcarboxy-2-chloroacetamidrazone.

Applicants respectfully request that the Examiner consider the disclosure in U.S. Patent No. 5,719,147 that teaches away from using the solvents dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, acetonitrile, N,N-dimethylacetamide or hexamethylphosphoramide. In particular, Example 75 of U.S. Patent No. 5,719,147 teaches away from the present invention which uses the solvent dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, acetonitrile, N,N-dimethylacetamide and hexamethylphosphoramide by indicating that acetonitrile should be employed for the alkylation reaction.

Even if one of ordinary skill in the art had been motivated to alter the process disclosed in U.S. Patent No. 5,719,147, there would have been no direction in U.S. Patent No. 5,719,147 regarding which specific reagents, solvents, temperature, additional steps and/or other conditions should have been employed in the process. From the discussion above, it is clear that one of ordinary skill in the art would not have simply had to choose from a finite number of identified, predictable solutions, with a reasonable expectation of success. One of ordinary skill in the art would not have had good reason to pursue a particular course of options to arrive at the claimed invention. As noted above, the disclosure of U.S. Patent No. 5,719,147 actually would have taught one of ordinary skill in the art away from the claimed invention. Applicants respectfully submit that U.S. Patent No. 5,719,147 taken as a whole would not have provided teaching and/or direction and motivation for the particular conditions employed in each of the claimed reaction steps

Accordingly, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness.

Unexpected Results

Applicants respectfully submit that even if the Examiner has established a prima facie case of obviousness, the present invention provides secondary indicia of non-obviousness, such as unexpected results relative to the disclosure of U.S. Patent No. 5,719,147. As noted in the specification (page 1, lines 14-19), the present invention provides a more practical and economical method for preparing the desired compound. As noted in the specification (page 7, lines 12-13), the present invention further provides an efficient process for preparing the desired compound that also minimizes the use of toxic solvents. Surprisingly, the present invention also gives the desired compound in 85% yield (page 8, lines 8-9), which is unexpectedly higher than the yield disclosed for the procedure in U.S. Patent No. 5,719,147 (79% yield) (Example 75, column 104).

Applicants respectfully submit that they have provided a showing that such results were greater than those which would have been expected from the prior art to an unobvious extent and that the results are of a significant, practical advantage.

By actual numerical advantage the claimed process provides the desired compound in 85% yield which is higher than the 79% yield disclosed in the prior art. This numerical advantage is particularly advantageous in the context of large-scale synthesis of the desired pharmaceutical product. In addition, the claimed process provides a more efficient process for preparing the desired compound by reducing the number of manipulations and steps relative to the process disclosed in the prior art. In addition, the claimed process provides a more environmentally-friendly process for preparing the desired compound by minimizing the use of toxic solvents relative to the process disclosed in the prior art.

Accordingly, Applicants respectfully submit that the rejection of Claims 28-46 and under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147) is untenable and should be withdrawn.

Applicants note that on February 27, 2009, the assignee of the subject patent application, Merck & Co. Inc., filed a Complaint in the U.S. District Court for the District of New Jersey against Sandoz Inc. alleging infringement of U.S. Patent Nos. 5,719,147, 6,048, 859, 6,096,742 and 6,235,735 with respect to Sandoz's FDA Abbreviated New Drug Application No. 90-999 which seeks approval to manufacture, use and sell 40 mg, 80 mg, and 125 mg aprepitant capsules prior to the expiration of such patents.

If an Interview with the Examiner would facilitate examination of the application, Applicants respectfully request that the Examiner contact their representative below.

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Applicants respectfully contend that the application is allowable and a favorable response from the Examiner is earnestly solicited.

Respectfully submitted,

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